Journal of the American College of Cardiology Vol. 48, No. 4, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.045

EXPEDITED REVIEW

Effects of Normal, Pre-Hypertensive, and Hypertensive Blood Pressure Levels on Progression of Coronary Atherosclerosis

Ilke Sipahi, MD,* E. Murat Tuzcu, MD, FACC,* Paul Schoenhagen, MD,† Katherine E. Wolski, MPH,* Stephen J. Nicholls, MBBS, PHD, FACC,* Craig Balog, BS,* Timothy D. Crowe, BS,* Steven E. Nissen, MD, FACC*

Cleveland, Ohio

OBJECTIVES The purpose of this study was to evaluate the effects of normal blood pressure (BP), pre-hypertension, and hypertension on progression of coronary atherosclerosis.

BACKGROUND The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) classifies BP as normal, pre-hypertension, and hypertension. The effects of these categories on progression of coronary atherosclerosis are unknown.

METHODS The 274 patients who completed the intravascular ultrasound (IVUS) substudy of the CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) trial were included. The entry criteria were ≥1 angiographic coronary stenosis >20% and diastolic BP <100 mm Hg. Patients underwent a baseline coronary IVUS, which was repeated after 2 years of amlodipine, enalapril, or placebo therapy. The BP was evaluated periodically, and the averages of the measurements were used in the analyses.

RESULTS Mean BP throughout the study was 127.0 ± 12.0/75.5 ± 6.8 mm Hg. In multivariable analysis, significant determinants of progression included systolic BP ($r = 0.16$; $p = 0.006$) and pulse pressure ($r = 0.14$; $p = 0.02$). Patients with "hypertensive" average BP had a 12.0 ± 3.6 mm^3 (least-square mean ± SE) increase in atheroma volume, those with "pre-hypertensive" BP had no major change (0.9 ± 1.8 mm^3), and those with "normal" BP had a decrease of 4.6 ± 2.6 mm^3 ($p < 0.001$ by analysis of covariance; $p < 0.05$ for comparison of all pairs).

CONCLUSIONS The most favorable rate of progression of coronary atherosclerosis is observed in patients whose BP falls within the "normal" JNC-7 category (i.e., systolic BP <120 mm Hg and diastolic BP <80 mm Hg). This study suggests that in patients with coronary artery disease, the optimal BP goal may be substantially lower than the <140/90 mm Hg level. (J Am Coll Cardiol 2006;48:833–8) © 2006 by the American College of Cardiology Foundation

Hypertension is an extremely common disease, affecting approximately 1 billion people worldwide (1). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), defined a new entity, "pre-hypertension," to reflect the growing evidence that systolic blood pressure (SBP) values between 120 and 139 mm Hg and diastolic blood pressure (DBP) values between 80 and 89 mm Hg are associated with increased cardiovascular risk (2). It is estimated that an additional 30% of the adult population fall into this category (3). However, few clinical trials have examined patients with blood pressure (BP) levels in the pre-hypertensive range, precluding any definitive recommendations for the treatment of this population. Therefore, in JNC-7, the therapeutic BP target for the general population remained at <140/90 mm Hg.

See page 839

Coronary artery disease is the most common form of target-organ damage and most common cause of mortality associated with hypertension. Although several studies have examined the relationship between hypertension on coronary events, and some have extended these observations to the "pre-hypertension" range (4), no prior data exist regarding the impact of hypertension, pre-hypertension, and normal BP on progression of coronary atherosclerosis. Recently, intravascular ultrasound (IVUS) has been used successfully to study the effects of drug therapies on progression of coronary disease, including agents that reduce low-density lipoprotein (LDL) cholesterol and C-reactive protein or modulate high-density lipoprotein (HDL) cholesterol (5–7). Although invasive, IVUS permits precise

*From the Department of Cardiovascular Medicine and the †Departments of Cardiovascular Medicine and Diagnostic Radiology, Cleveland Clinic Foundation, Cleveland, Ohio. The CAMELOT study was funded by Pfizer. A Ralph Reader Overseas Research Fellowship from the National Heart Foundation of Australia supports Dr Nicholls. Dr. Sipahi has received an educational grant from Pfizer. Dr. Tuzcu has received research support and lecture honoraria from Pfizer. Dr. Nicholls has received lecture honoraria from Pfizer. Dr. Nissen has received research support from and is an unpaid consultant to Pfizer.

Manuscript received March 3, 2006; revised manuscript received April 18, 2006, accepted May 15, 2006.

Abbreviations and Acronyms

BP	= blood pressure
CAMELOT	= Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis trial
DBP	= diastolic blood pressure
HDL	= high-density lipoprotein
IVUS	= intravascular ultrasound
JNC-7	= Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LDL	= low-density lipoprotein
LOWESS	= locally weighted scatterplot smoothing
SBP	= systolic blood pressure

measurement of atheroma burden at baseline and follow-up, enabling calculation of progression rate of atherosclerosis. The CAMELOT (Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis) trial enrolled coronary disease patients with a mean BP of 129/78 mm Hg and included an IVUS substudy that assessed the change in atherosclerotic disease burden during the 2-year follow-up (8). In the present analysis, our objective was to examine the effects of components of BP (SBP, DBP, and pulse pressure) and the JNC-7 BP categories on coronary disease progression in the CAMELOT trial.

METHODS

Study population. The CAMELOT trial was a multicenter double-blinded randomized trial that compared the effects of amlodipine up to 10 mg/day versus enalapril up to 20 mg/day versus placebo on cardiovascular event rates in patients with coronary artery disease (8). The study enrolled men and women age 30 to 79 years who required coronary angiography for clinical indications and demonstrated at least 1 obstruction with angiographic diameter stenosis of >20%. Study eligibility required a DBP <100 mm Hg with or without treatment. There were 1,997 patients enrolled in the CAMELOT trial, and 274 of them completed the IVUS substudy. The Cleveland Clinic Institutional Review Board approved research using this database.

IVUS. Subjects enrolled in the IVUS substudy underwent a baseline ultrasound interrogation before randomization. The acquisition and measurement methodology of IVUS atherosclerosis progression-regression trials have been described in detail elsewhere (6,7). Briefly, after administration of intracoronary nitroglycerin, the IVUS catheter was advanced into the target vessel and the transducer was positioned distal to a side branch (distal fiduciary site). The target vessel for the IVUS interrogation (a single coronary artery per patient) must not have undergone percutaneous intervention or have an angiographic diameter stenosis of >50%. A motor drive unit progressively withdrew the transducer at a speed of 0.5 mm/s. During pullback, images were obtained at 30 frames/s and were recorded on videotape for off-line analysis. After digitization of the videotapes, measurements of external elastic membrane (EEM) and lumen areas were performed in accordance with the standards of the American College of Cardiology (9). Measurements were performed at every 60th frame (i.e., every 1 mm) starting at the distal branch site and ending at a proximal branch site. Follow-up IVUS was performed in the same arterial segments after a 24-month treatment regimen consisting of amlodipine, enalapril, or placebo.

Calculation of end points. Atheroma volume was calculated as: Σ(EEM area − lumen area), which corresponded to the sum of the atheroma areas in slices spaced 1 mm apart. To compensate for pullbacks of differing lengths, "normalized atheroma volume" was used in the analyses, calculated as:

$$\left(\frac{\text{atheroma volume}}{\text{number of measured images}}\right) \times \text{mean number of images for all pullbacks}$$

BP and lipid profile measurements. The BP was measured at baseline, at the first month, and every 3 months thereafter. Measurements were taken after the patient had been seated for 3 min and then repeated 2 min later. The 2 values were averaged at each visit. Pulse pressure was calculated as: SBP − DBP. For each BP component, the mean value observed throughout the study period was calculated by averaging the values obtained at each visit except the baseline visit. The BP was categorized as "hypertensive" if mean SBP was ≥140 mm Hg or mean DBP was ≥90 mm Hg, as "pre-hypertensive" if mean SBP was 120 to 139 mm Hg or mean DBP was 80 to 89 mm Hg, and as "normal" if mean SBP was <120 mm Hg and mean DBP was <80 mm Hg (2). A central laboratory measured the lipid profile at baseline and every 6 months, and mean lipid levels throughout the study were calculated in a similar fashion to the mean BP.

Data analysis. Analyses were performed with SPSS 11.5 for Windows (SPSS Inc., Chicago, Illinois). General characteristics of patients are summarized using mean ± SD for continuous data and number (%) for categorical data. Baseline and follow-up IVUS data are presented as mean ± SD and median (interquartile range) owing to the nonnormal distribution of these variables. Relationships were assessed by multiple linear regression analysis and partial correlation coefficients were obtained. Since many variables (e.g., atheroma volumes, lipid parameters, pulse pressure) were not normally distributed, rank transformed data were used in the regression analyses. For plotting the relationships between BP and change in atheroma volume, locally weighted scatterplot smoothing (LOWESS) technique was used. For comparing the baseline atheroma volume among the JNC-7 BP categories, the nonparametric Kruskal-Wallis test was used. Analysis of covariance was used to examine the impact of the JNC-7 BP categories on the progression rate, and least-square means ± SE were ob-

Table 1. Characteristics of Patients With Normal, Pre-Hypertensive, and Hypertensive Average Blood Pressure Levels During the Study

Characteristic	Normal (n = 76)	Pre-Hypertensive (n = 157)	Hypertensive (n = 41)	p Value*
Age, yrs	53.0 ± 8.4	57.5 ± 9.4	61.9 ± 10.5	<0.001
Male	65 (85.5%)	123 (78.3%)	27 (65.8%)	0.047
Body mass index, kg/m^2	29.4 ± 4.4	30.2 ± 4.8	31.3 ± 6.3	0.15
Current smoker	19 (25.0%)	37 (23.5%)	9 (21.9%)	0.90
History of hypertension	33 (43.4%)	110 (70.0%)	32 (78.0%)	<0.001
History of diabetes	10 (13.1%)	31 (19.7%)	6 (14.6%)	0.41
Lipid profile†				
Total cholesterol, mg/dl	183.2 ± 27.6	179.9 ± 34.7	173.7 ± 41.1	0.35
LDL cholesterol, mg/dl	100.0 ± 22.2	98.2 ± 27.8	94.6 ± 37.4	0.64
HDL cholesterol, mg/dl	41.1 ± 11.1	41.2 ± 11.7	44.4 ± 14.7	0.28
Triglycerides, mg/dl	194.1 ± 97.3	185.9 ± 118.1	170.5 ± 95.1	0.13
LDL/HDL cholesterol ratio	2.6 ± 0.8	2.6 ± 1.1	2.2 ± 0.8	0.07
Study medications				0.02
Amlodipine	26 (34.2%)	56 (35.6%)	9 (21.9%)	
Enalapril	33 (43.4%)	42 (26.7%)	13 (31.7%)	
Placebo	17 (22.3%)	59 (38.0%)	19 (46.3%)	
Concomitant medications				
Aspirin	75 (98.6%)	150 (95.5%)	38 (92.6%)	0.26
Beta-blocker	57 (75.0%)	134 (85.3%)	34 (82.9%)	0.15
Statin	66 (86.8%)	140 (89.1%)	34 (82.9%)	0.54

*p values for continuous variables were obtained with analysis of variance except for triglycerides and LDL/HDL cholesterol ratio for which the Kruskal-Wallis test was used. The p values for categorical variables were obtained with the chi-square test; †average values during the study period.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

tained. Pair-wise comparisons between the 3 JNC-7 categories were not adjusted for multiple comparisons. Two-sided p values of <0.05 were considered significant.

RESULTS

Study population. In the total study population of 274 patients, the baseline BP was similar to the full CAMELOT trial cohort: 129.9 ± 15.6/77.2 ± 8.4 mm Hg. Because about two-thirds of the patients were on active treatment arms, BP was significantly decreased at the 24-month follow-up: 126.2 ± 15.8/75.1 ± 10.2 mm Hg. Mean on-treatment BP throughout the study period was 127.0 ± 12.0/75.5 ± 6.8 mm Hg.

According to the classification criteria of the JNC-7, 76 patients (27.7%) had mean on-treatment BP levels within the normal range (on average 114/71 mm Hg), 157 (57.3%) within the pre-hypertensive range (on average 128/76 mm Hg), and 41 (15%) within the hypertensive range (on average 147/80 mm Hg). The characteristics of patients with normal, pre-hypertensive, and hypertensive BP levels are presented in Table 1. Patients with higher BP levels were older, more likely to be female, and, predictably, more likely to have a history of hypertension. Patients with lower blood pressure levels showed trends for having higher LDL/HDL cholesterol ratios and higher triglyceride levels. Patients with lower average BP levels were more commonly allocated to the active treatment arms consisting of amlodipine and enalapril. The frequency of concomitant statin treatment was similar among the 3 categories.

Determinants of progression of coronary artery disease. There was no relationship between age, gender, body mass index, current smoking status, diabetes, and change in atheroma volume (Table 2). Total cholesterol, LDL cholesterol, and triglycerides trended toward a positive correlation and HDL cholesterol toward a negative correlation with change in atheroma volume. The LDL/HDL cholesterol ratio was the strongest determinant of change in atheroma volume (r = 0.18; p = 0.003).

Among components of BP, mean SBP correlated significantly with change in atheroma volume (r = 0.14; p = 0.02). There was no significant relationship between

Table 2. Relationships Between Patient Characteristics and Change in Atheroma Volume*

	Correlation Coefficient	p Value
Age	0.04	0.53
Male gender	−0.004	0.95
Body mass index	0.02	0.69
Current smoking	0.02	0.81
History of hypertension	0.12	0.05
History of diabetes	−0.06	0.35
Lipid profile		
Total cholesterol	0.10	0.11
LDL cholesterol	0.10	0.09
HDL cholesterol	−0.11	0.07
Triglycerides	0.11	0.06
LDL/HDL cholesterol ratio	0.18	0.003
BP components		
SBP	0.14	0.02
DBP	0.09	0.15
Pulse pressure	0.11	0.06

*Based on rank transformed data and adjusted for baseline atheroma volume. For lipid parameters and blood pressure components, average values throughout the study period were used. Since 2 patients had incomplete laboratory data, the results of 272 patients are shown for the lipid parameters.
DBP = diastolic blood pressure; SBP = systolic blood pressure; other abbreviations as in Table 1.

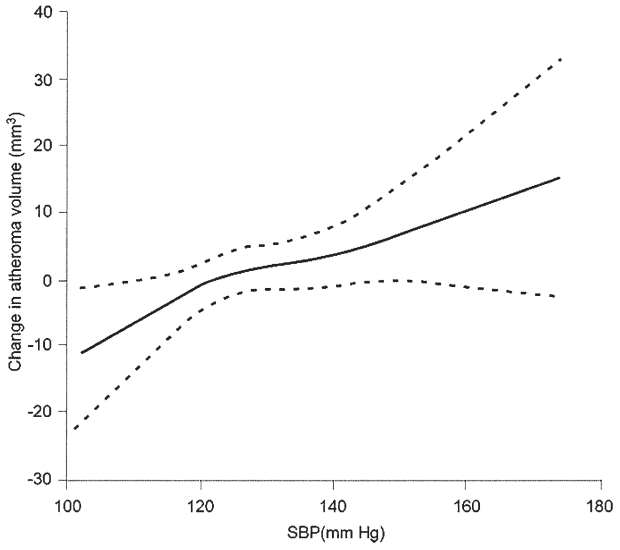

Figure 1. Locally weighted scatterplot smoothing graph showing the relationships between systolic blood pressure (SBP) and the rate of progression of coronary atherosclerosis (n = 274). An SBP in the range of approximately 120 to 140 mm Hg corresponded to no net progression or regression of coronary disease. Values above this range were associated with progression and those below were associated with regression of disease.

DBP and change in atheroma volume (r = 0.09; p = 0.15). Figure 1 shows the LOWESS graph for the relationship between SBP and progression rate of coronary atherosclerosis.

Multivariable analysis was performed to control for possible confounding variables. Mean on-treatment LDL/HDL cholesterol ratio and triglycerides were included in these models because they were related to both the predictor variable (BP) and the outcome variable (disease progression). In this type of analysis, mean SBP remained as a significant predictor of change in atheroma volume (r = 0.16; p = 0.006) (Table 3). There was still no significant relationship between DBP and change in atheroma volume. However, there was a significant correlation between pulse pressure and change in atheroma volume in multivariable analysis.

Table 3. Relationships Between Blood Pressure Components and Change in Atheroma Volume on Multivariable Analysis*

	Correlation Coefficient	p Value
SBP	0.16	0.006
DBP	0.08	0.16
Pulse pressure	0.14	0.02

*Based on rank transformed data and adjusted for baseline atheroma volume, LDL/HDL cholesterol ratio, and triglycerides. For each blood pressure component, the average value observed throughout the study period was used. Since 2 patients had incomplete laboratory data, the results of 272 patients are shown.
Abbreviations as in Tables 1 and 2.

Although mean on-treatment BP levels significantly correlated with the progression rate, the changes in the BP components from baseline to follow-up did not correlate with change in atheroma volume (p > 0.30 for all).

JNC-7 categories and progression rate. The IVUS findings of patients with normal, pre-hypertensive, and hypertensive average BP levels are presented in Table 4. There was no significant difference in the atheroma volumes of the 3 categories at baseline (p = 0.29). However, the progression rate of atherosclerosis was significantly different among these categories (p < 0.001 by analysis of covariance). Accordingly, hypertensive subjects had an increase in adjusted atheroma volume of 12.0 mm^3 (p = 0.001 compared with baseline), pre-hypertensive subjects had no major change (0.9 mm^3; p = 0.61 compared with baseline), and subjects with normal BP had a decrease in atheroma volume of 4.6 mm^3 (p = 0.08 compared with baseline) (p < 0.05 for all pair-wise comparisons) (Fig. 2). These findings were not different after additional adjusting for allocation to amlodipine and enalapril arms (p < 0.001 by analysis of covariance; p < 0.05 for all pair-wise comparisons). Additionally, there was no significant interaction between either amlodipine or enalapril treatment and the effects of BP categories on the progression rate (p = 0.20 and p = 0.46, respectively).

There were 42 patients who moved from the pre-hypertension category at baseline to the normal BP category during the study, of which 32 were on an active treatment

Table 4. Intravascular Ultrasonographic Measures of Atheroma Burden in Patients With Normal, Pre-Hypertensive, and Hypertensive Average Blood Pressure Levels During the Study

	Normal (n = 76)	Pre-Hypertensive (n = 155)	Hypertensive (n = 41)	p Value
Baseline atheroma volume (mm^3)				
Mean ± SD	187.9 ± 79.5	190.8 ± 81.6	202.2 ± 61.7	0.29*
Median (interquartile range)	180.8 (133.1–238.1)	171.7 (137.4–241.2)	205.4 (158.7–250.9)	
Follow-up atheroma volume (mm^3)				
Mean ± SD	184.5 ± 74.6	191.7 ± 82.0	211.5 ± 64.7	0.001†
Median (interquartile range)	168.2 (129.3–238.4)	179.5 (133.1–227.3)	212.2 (155.2–259.9)	
p value‡ (compared to baseline)	0.08	0.61	0.001	
Change in atheroma volume (mm^3)				
Least-square mean ± SE	−4.6 ± 2.6	0.9 ± 1.8	12.0 ± 3.6	<0.001†

*Kruskal-Wallis test; †analysis of covariance model with rank-transformed baseline values, LDL/HDL cholesterol ratio and triglycerides as covariates; ‡analysis of covariance model with rank-transformed LDL/HDL cholesterol ratio and triglycerides as covariates. Since 2 patients had incomplete plasma lipid data, the results of a total of 272 patients are shown.
Abbreviations as in Tables 1 and 2.

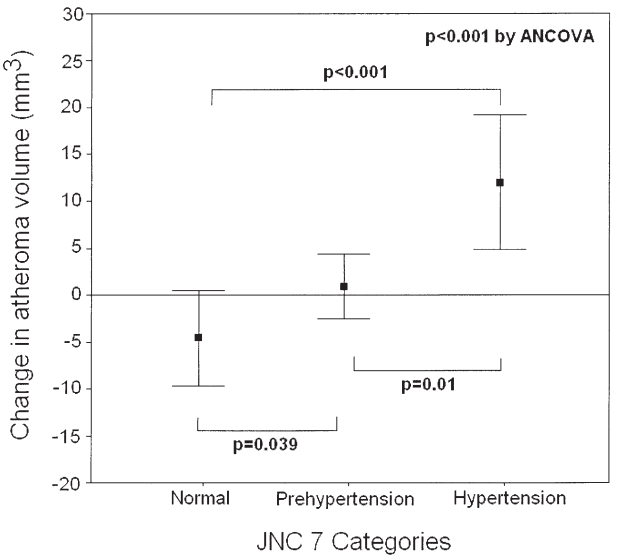

Figure 2. Progression rate of coronary artery disease according to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) blood pressure categories. **Error bars** represent means and 95% confidence intervals. *The p values were obtained using rank transformed data and adjusting for baseline total atheroma volume, low-density lipoprotein (LDL)/high-density lipoprotein (HDL) cholesterol ratio, and triglycerides. ANCOVA = analysis of covariance.

arm. In contrast, 121 patients remained in the pre-hypertension category from baseline to follow-up. The progression rate was significantly lower in the group that had transition from pre-hypertension to normal BP (6.2 ± 3.6 mm^3 [mean ± SE] decrease in atheroma volume) compared with the group who remained pre-hypertensive (1.5 ± 2.1 mm^3 increase in atheroma volume; p = 0.037 by analysis of covariance).

DISCUSSION

The study demonstrates a continuous relationship between SBP and the progression rate of coronary atherosclerosis over a broad range of blood pressures extending from 100 mm Hg to the hypertensive range.

Hypertension is usually defined as a systolic pressure above 140 mm Hg and/or a diastolic pressure above 90 mm Hg. It represents a strong risk factor for coronary and noncoronary cardiovascular events and mortality. Accumulating evidence has suggested that there is no threshold BP value below which cardiovascular risk does not decrease, with optimal event rates observed for levels below 115/75 mm Hg (4). Consonant with these observations, the World Health Organization has reported that a suboptimal BP (i.e., SBP >115 mm Hg) represents the number 1 attributable risk for death throughout the world. In light of this evidence, the JNC-7 classification of BP introduced a new category called "pre-hypertension" (defined as a systolic pressure between 120 and 139 mm Hg or a diastolic pressure between 80 and 89 mm Hg) to emphasize the increased cardiovascular risk and the high likelihood of progression to frank hypertension. However, in the absence of randomized clinical trials, JNC-7 recommends only lifestyle modifications without drug therapy for pre-hypertension, unless the patient has concomitant diabetes or chronic kidney disease and a blood pressure above 130/80 mm Hg. Likewise, in other patients with established hypertension, the therapeutic BP goal remains <140/90 mm Hg.

Coronary artery disease is the most common target organ damage noted as a result of hypertension and the most important cause of mortality in hypertensive patients. The present study demonstrates that in patients with coronary artery disease and "acceptable" BP levels by current standards (127/76 mm Hg on average), SBP is still a significant determinant of disease progression. Comparison of patients in the different JNC-7 categories revealed that those with "hypertensive" BP levels have the worst outcome (a 12 mm^3 increase in atheroma volume on an arterial segment of approximately 30 mm in 2 years), those with "pre-hypertensive" BP have an intermediate outcome (an increase of 0.9 mm^3), and those with "normal" BP have the best outcome, showing a trend for disease regression (a 4.6 mm^3 reduction in atheroma volume). Patients who improved from a pre-hypertensive BP level at baseline to normal BP levels during the study had significantly less progression of atheroma than patients who remained pre-hypertensive.

These findings are consistent with epidemiologic data demonstrating that coronary event rates are highest in those with hypertension, intermediate in those with pre-hypertension, and lowest in those with normal BP (10,11). Although the JNC-7 sets lower BP goals for patients with diabetes and chronic kidney disease, the target BP levels in patients with coronary artery disease are not different from recommendations for the general population. Our findings suggest that optimal BP for patients with coronary artery disease is substantially lower than the <140/90 mm Hg level and may be as low as <120/80 mm Hg. Patients achieving a normal BP (on average 114/71 mm Hg) actually showed a strong trend toward regression, a finding previously demonstrated only for aggressive interventions such as infusion of an HDL mimetic (7).

The relationship between BP and coronary disease progression was independent of the study treatments consisting of enalapril, an angiotensin-converting enzyme inhibitor, and amlodipine, a calcium-channel blocker. This demonstrates that for slowing progression of coronary atherosclerosis, the absolute BP level attained is a crucial parameter, regardless of the particular BP-lowering drug used.

The current study adds mechanistic insights regarding the relationship between BP components and clinical event rates. Systolic pressure appears to be an important component for progression of coronary atherosclerosis. This finding complements the studies reporting on the strong relationship between SBP and coronary events (12–17). Studies relating DBP and pulse pressure to cardiovascular event rates have yielded mixed results (12–15,18–22). In this context, our study specifically excluded patients with a

diastolic pressure >100 mm Hg. Therefore our finding of no significant relationship between DBP and disease progression should be interpreted with caution. It is possible that higher DBP levels may have a different relationship to disease progression. Moreover, narrowing the range of DBP may have reduced its predictive ability by reducing its variance.

Study limitations. This study examined a group of patients with existing coronary disease, not a general hypertensive population. Thus, no conclusion regarding the optimal BP can be drawn from this study for primary prevention patients. Most of the enrolled patients were white and middle aged. Therefore, our findings may not apply to other races or age groups.

Conclusions. In a patient population with well controlled BP and coronary artery disease, a higher SBP level is associated with greater progression of coronary atherosclerosis. Normal BP (i.e., SBP <120 mm Hg and DBP <80 mm Hg) is the most favorable JNC-7 BP category to slow progression or induce regression of coronary artery disease. For secondary prevention of coronary artery disease, the current IVUS study demonstrates that optimal outcomes are attained for patients reaching a BP goal substantially lower than the <140/90 mm Hg level advocated in the current guidelines.

Acknowledgments

The authors thank William A. Magyar, Jay E. Zhitnik, Aaron Loyd, and Tammy Churchill at the Cleveland Clinic Foundation Intravascular Ultrasound Core Laboratory for their technical support in this study. The authors acknowledge the contributions made by David J. Frid, Harry Shi, and Kamlesh M. Thakker, from Pfizer.

Reprint requests and correspondence: Dr. Steven E. Nissen, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: nissens@ccf.org.

REFERENCES

1. World Health Report 2002. Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization, 2002. Available at: http://www.who.int/whr/2002. Accessed June 12, 2006.
2. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report. JAMA 2003;289:2560–72.
3. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among U.S. adults according to the new joint national committee guidelines: new challenges of the old problem. Arch Intern Med 2004;164:2126–34.
4. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903–13.
5. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
6. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291:1071–80.
7. Nissen SE, Tsunoda T, Tuzcu EM, et al. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA 2003;290: 2292–300.
8. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004;292:2217–25.
9. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001;37:1478–92.
10. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA 2005;294:466–72.
11. Qureshi AI, Suri MF, Kirmani JF, Divani AA, Mohammad Y. Is prehypertension a risk factor for cardiovascular diseases? Stroke 2005; 36:1859–63.
12. Mitchell GF, Moye LA, Braunwald E, et al., SAVE Investigators. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Circulation 1997; 96:4254–60.
13. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–60.
14. Miura K, Dyer AR, Greenland P, et al. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: the Chicago Heart Association Detection Project in Industry study. Hypertension 2001;38:232–7.
15. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation 2001;103:1245–9.
16. Mattace-Raso FU, van der Cammen TJ, van Popele NM, et al. Blood pressure components and cardiovascular events in older adults: the Rotterdam study. J Am Geriatr Soc 2004;52:1538–42.
17. Nair GV, Chaput LA, Vittinghoff E, Herrington DM. Pulse pressure and cardiovascular events in postmenopausal women with coronary heart disease. Chest 2005;127:1498–506.
18. Benetos A, Rudnichi A, Safar M, Guize L. Pulse pressure and cardiovascular mortality in normotensive and hypertensive subjects. Hypertension 1998;32:560–4.
19. Benetos A, Thomas F, Safar ME, Bean KE, Guize L. Should diastolic and systolic blood pressure be considered for cardiovascular risk evaluation: a study in middle-aged men and women. J Am Coll Cardiol 2001;37:163–8.
20. Lee ML, Rosner BA, Weiss ST. Relationship of blood pressure to cardiovascular death: the effects of pulse pressure in the elderly. Ann Epidemiol 1999;9:101–7.
21. Khattar RS, Swales JD, Dore C, Senior R, Lahiri A. Effect of aging on the prognostic significance of ambulatory systolic, diastolic, and pulse pressure in essential hypertension. Circulation 2001;104:783–9.
22. Domanski M, Mitchell G, Pfeffer M, et al. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 2002;287: 2677–83.